IL FOLLOW-UP A LUNGO TERMINE CONFERMA BENEFICI CLINICI DURATURI CON EXAGAMGLOGENE AUTOTEMCEL NELLA β-TALASSEMIA TRASFUSIONE-DIPENDENTE: RISULTATI FINALI DELLO STUDIO CLIMB THAL-111

Franco Locatelli,[1] Haydar Frangoul,[2] Selim Corbacioglu,[3] Josu de la Fuente,[4] Peter Lang,[5] Mattia Algeri,[6] Joachim Rupprecht,[5] Kevin H. M. Kuo,[7] Melanie Kirby-Allen,[8] Amanda M. Li,[9] Ami J. Shah,[10] Markus Mapara,[11] Ben Carpenter,[12] Robert I. Liem,[13] Janet L. Kwiatkowski,[14] Hayley Merkeley,[15] Stephan A. Grupp,[14] Maria Domenica Cappellini,[16] Antonis Kattamis,[17] Sujit Sheth,[18] Kathleen Lee-Sarwar,[19] Bo Tong,[19] Sakellarios Zairis,[19] William Hobbs,[19] Roland Meisel[20]

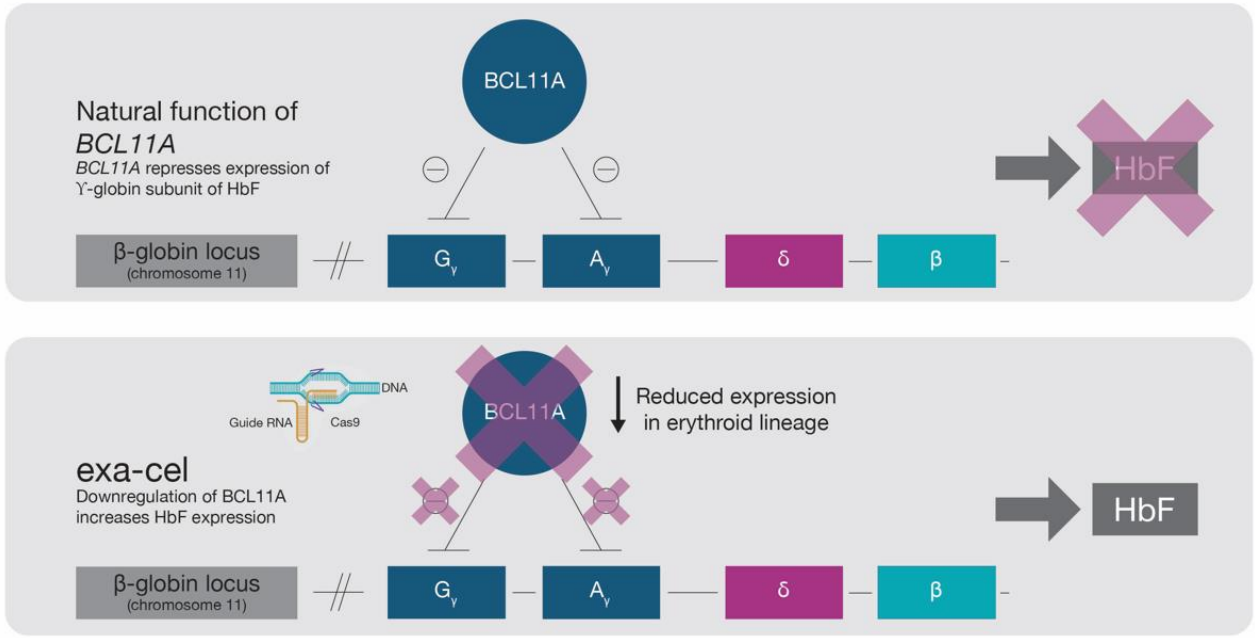
[1]IRCCS, Ospedale Pediatrico Bambino Gesù Rome, Catholic University of the Sacred Heart, Rome, Italy; [2]Sarah Cannon Research Institute at The Children's Hospital at TriStar Centennial, Nashville, TN, USA; [3]University of Regensburg, Regensburg, Germany; [4]Imperial College Healthcare NHS Trust, St Mary's Hospital, London, UK; [5]University of Tübingen, Tübingen, Germany; [6]IRCCS, Ospedale Pediatrico Bambino Gesù Rome, Italy; [7]Division of Hematology, University of Toronto, Toronto, Canada; [8]Hospital for Sick Children, Toronto, Canada; [9]BC Children's Hospital, University of British Columbia, Vancouver, Canada; [10]Stanford University, Palo Alto, CA, USA; [11]Division of Hematology and Oncology, Columbia University, New York, NY, USA; [12]University College London Hospitals NHS Foundation Trust, London, UK; [13]Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA; [14]Children's Hospital of Philadelphia and Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [15]Department of Medicine, The University of British Columbia/Adult Red Cell Disorder Program of British Columbia, Vancouver, BC; [16]University of Milan, Milan, Italy; [17]National and Kapodistrian University of Athens, Athens, Greece; [18]Joan and Sanford I Weill Medical College of Cornell University, New York, NY, USA; [19]Vertex Pharmaceuticals Incorporated, Boston, MA, USA; [20]Division of Pediatric Stem Cell Therapy, Department of Pediatric Oncology, Hematology and Clinical Immunology, Medical Faculty, Heinrich-Heine-University, Düsseldorf, Germany

Disclosures of Franco Locatelli

Name of Company	Research Support	Employee	Consultant	Stockholder	Speaker's Bureau	Advisory Board	Other
Miltenyi					X		
Amgen					X	X	
Novartis					X	X	
BMS					X		
GILEAD					X		
MEDAC					X	X	
Sanofi						X	
SOBI					X		
Vertex					X	X	

Exa-cel (CASGEVY) is the First Approved CRISPR/Cas9 Gene Editing Therapy

- **Exa-cel (CASGEVY®)** is a **one-time, nonviral, *ex vivo,* CRISPR/CAS9 gene-edited autologous cell therapy** which is **approved** for treatment of patients with transfusion-dependent β-thalassemia (TDT) aged ≥2 years in the US and ≥12 years in other regions[1]
- Exa-cel Phase 3 clinical trial data have demonstrated **reactivation of the synthesis of HbF** to levels that **eliminate the need for transfusion in TDT**[2]
- We report **final results from CLIMB THAL-111** and data demonstrating **durable clinical benefit and correction of ineffective erythropoiesis** with a median follow-up of 4.5 years and a **longest follow-up of 6.9 years***



*Data are as of Nov 2025.

***BCL11A*,** B-cell lymphoma/leukemia 11A; **Cas9,** CRISPR-associated 9 nuclease; **CRISPR,** clustered regularly interspaced short palindromic repeats; **exa-cel,** exagamglogene autotemcel; **HbF,** fetal hemoglobin; **TDT,** transfusion-dependent β-thalassemia.

1. Refer to regional label for specific indication. **2.** Locatelli F, et al. *N Engl J Med*. 2024;390(18):1663-1676.

Exa-cel Pivotal Phase 3 Trial Design

CLIMB THAL-111 (NCT03655678): Study Complete	
Study Design	Global, multicenter, open-label, single-arm, 2-year Phase 1/2/3 trial of a single infusion of exa-cel
Participants	12 to 35 years of age with TDT defined as a history of ≥100 mL/kg/year or ≥10 units/year of RBC transfusions in the previous 2 years
Primary Efficacy Endpoint	**Proportion of participants who are transfusion independent for ≥12 consecutive months while maintaining a weighted average hemoglobin ≥9 g/dL (TI12)**
Secondary and Additional Efficacy Endpoints	• Duration of transfusion independence for participants who achieved TI12 • Total Hb and HbF levels • Allelic editing at the intended locus in bone marrow $CD34^+$ HSCs and peripheral blood cells • Measures of iron overload (serum ferritin, liver iron concentration[a], and cardiac iron content[b]) • Proportion of participants receiving iron removal therapy over time[c] • Measures of ineffective erythropoiesis in bone marrow (erythroferrone and hepcidin) • Patient-reported outcomes

CLIMB 131 (NCT04208529)
Global, multicenter, open-label, rollover Phase 3 trial to provide up to 15 years of long-term efficacy and safety follow-up

[a] Liver iron concentration measured by R2 MRI
[b] Cardiac iron content measured by T2* MRI
[c] Analysis included all types of iron removal therapy, including chelation and/or phlebotomy
exa-cel, exagamglogene autotemcel; **Hb,** hemoglobin; **HbF,** fetal hemoglobin; **HSCs,** hematopoietic stem cells; **RBC**, red blood cell; **TDT**, transfusion-dependent β-thalassemia; **TI12**, free from RBC transfusions for ≥12 consecutive months while maintaining a weighted average Hb ≥9 g/dL.

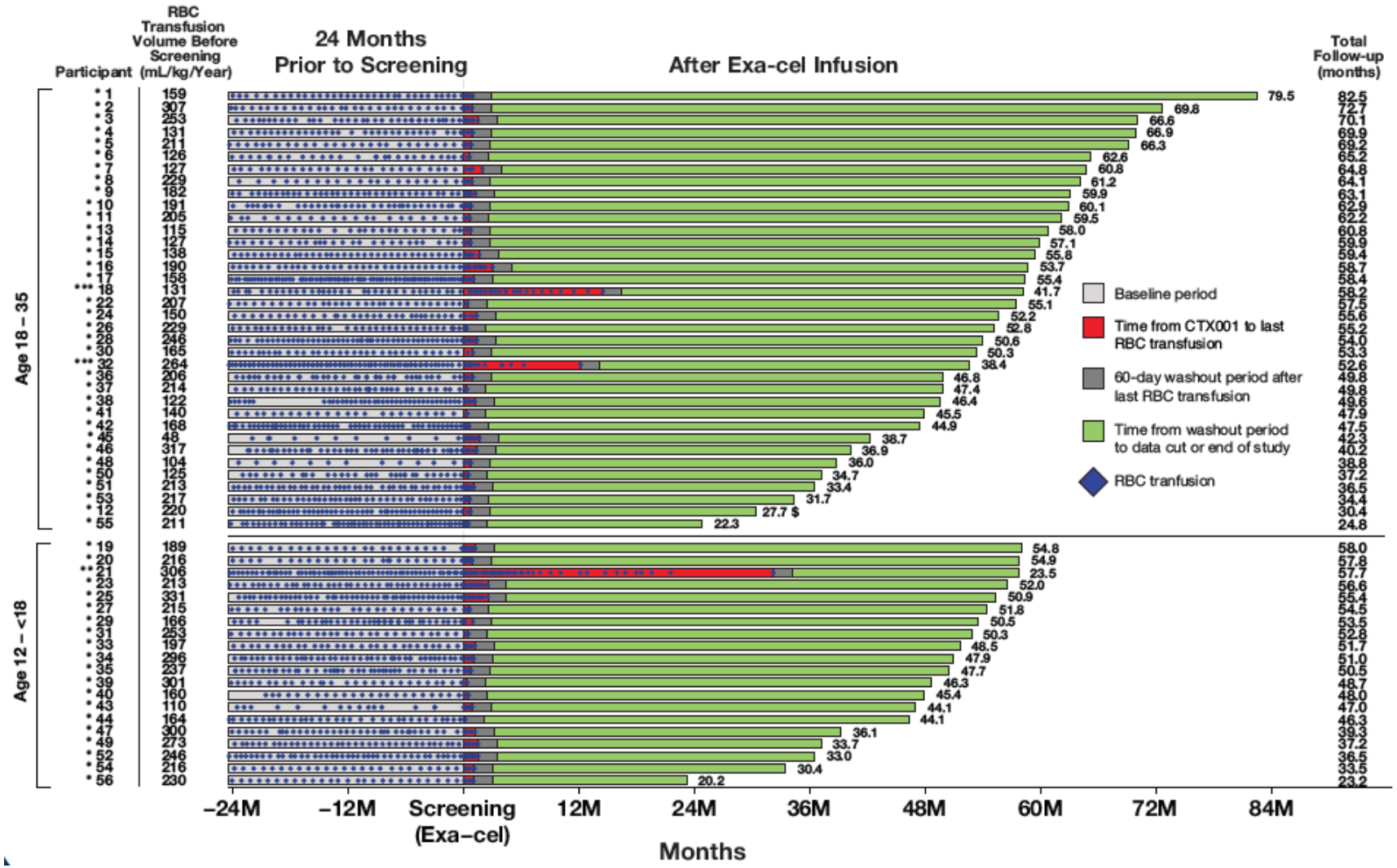
Key Demographics, Baseline Characteristics, and Treatment Features

	Full Analysis Set[a] N = 56
Age (years) at screening, mean (SD)	**21.2 (6.5)**
≥12 and <18 years, n (%)	20 (35.7)
≥18 and ≤35 years, n (%)	36 (64.3)
Genotype, n (%)	
β^0/β^0	22 (39.3)
β^0/β^0-like (β^0/IVS-I-110; IVS-I-110/IVS-I-110)	13 (23.2)
Non-β^0/β^0-like	21 (37.5)
Tissue iron overload measures at baseline	
Serum Ferritin (mg/L), median (range)	1280.5 (260.0, 4823.0)
Liver Iron Concentration (mg/g), median (range)	3.6 (1.2, 14.8)
Cardiac T2* (msec), median (range)	34.0 (12.4, 61.1)
Annualized volume of RBC transfusions (mL/kg), median (range)[b]	**206.7 (48.3, 330.9)**
Annualized units of RBC transfusions, median (range)[b]	**36.0 (11.0, 71.0)**
No. of mobilization/apheresis cycles needed for Drug Product, mean (range)	**1.3 (1, 4)**
Neutrophil engraftment (days)	
Time to neutrophil engraftment, median (range)	29.0 (12, 56)
Duration of neutropenia (absolute neutrophil count <500 cells/μL), median (range)	20.5 (4, 48)
Platelet engraftment (days)	
Time to platelet engraftment, median (range)	43.5 (20, 200)
Time (days) to hospital discharge, median (range)	**39.0 (23, 110)**
Duration (months) of follow-up[c] after exa-cel, median (range)	**53.4 (23.2, 82.5)**

[a] Includes all participants who received exa-cel infusion
[b] In the 2 years prior to enrollment
[c] Follow-up duration included CLIMB-131
exa-cel: exagamglogene autotemcel; **RBC:** red blood cell; **SD:** standard deviation.

Durable Transfusion Independence Achieved After Exa-cel (CLIMB THAL-111 and 131)

Transfusion independence achieved in 98% and maintained for up to 6.6 Years



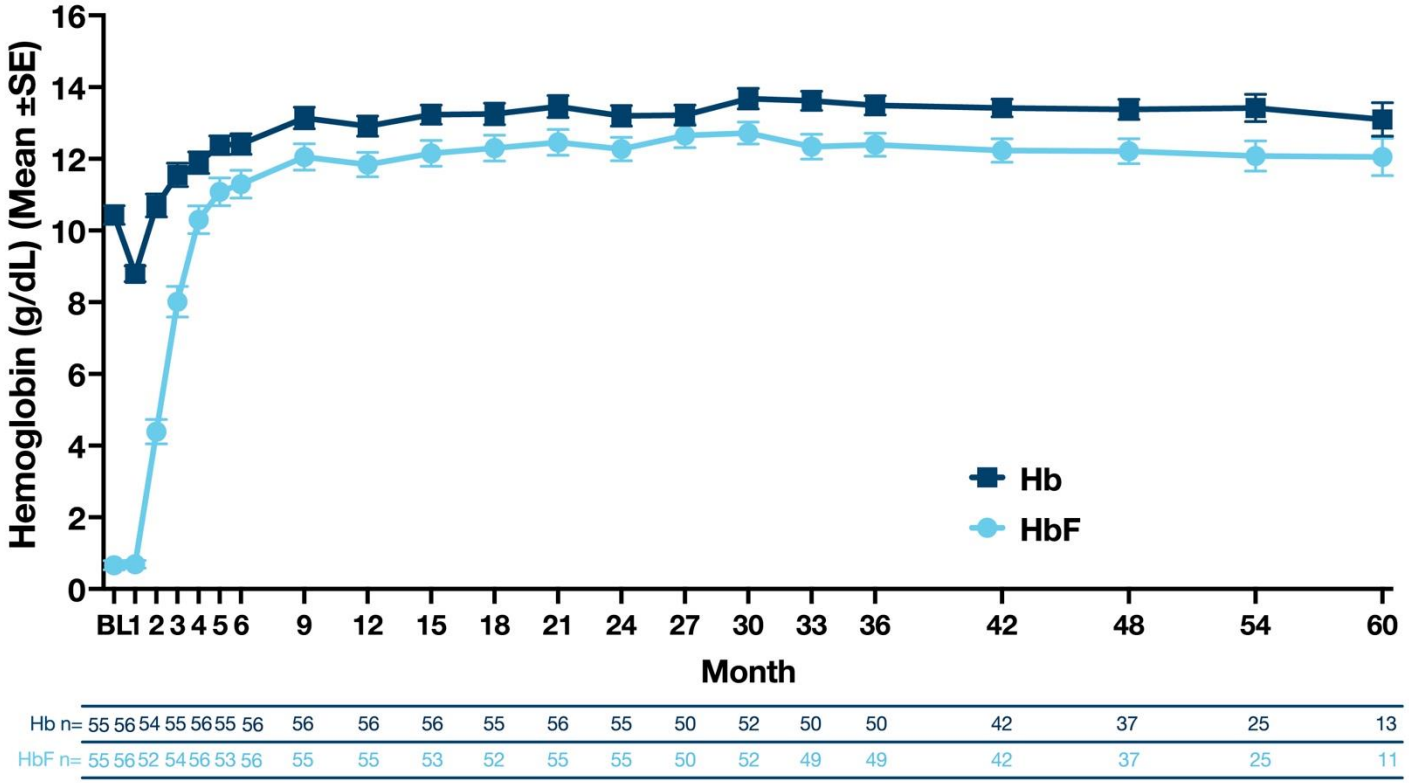
- **98% (55/56) of participants achieved TI12 in CLIMB THAL-111 and CLIMB-131 combined**
  - **Similar efficacy response observed in adults aged ≥18 years and adolescents aged ≥12 to <18 years**
- **Mean duration of transfusion independence is 4.0 years (range: 1.7 to 6.6)**
- **1 participant who has not yet achieved TI12 (weighted average Hb has not reached 9 g/dL for 12 months) has been transfusion-free for 2 years**

Data shown are as of Nov 2025

* Achieved TI12 in CLIMB THAL-111; **Did not achieve TI12 (due to not having weighted average Hb ≥9 g/dL); ***Achieved TI12 in CLIMB-131 only

EOS: end of study**; exa-cel:** exagamglogene autotemcel; **Hb:** hemoglobin; **RBC:** red blood cell; **TI12:** transfusion independent for ≥12 consecutive months while maintaining a weighted average Hb ≥9 g/dL.

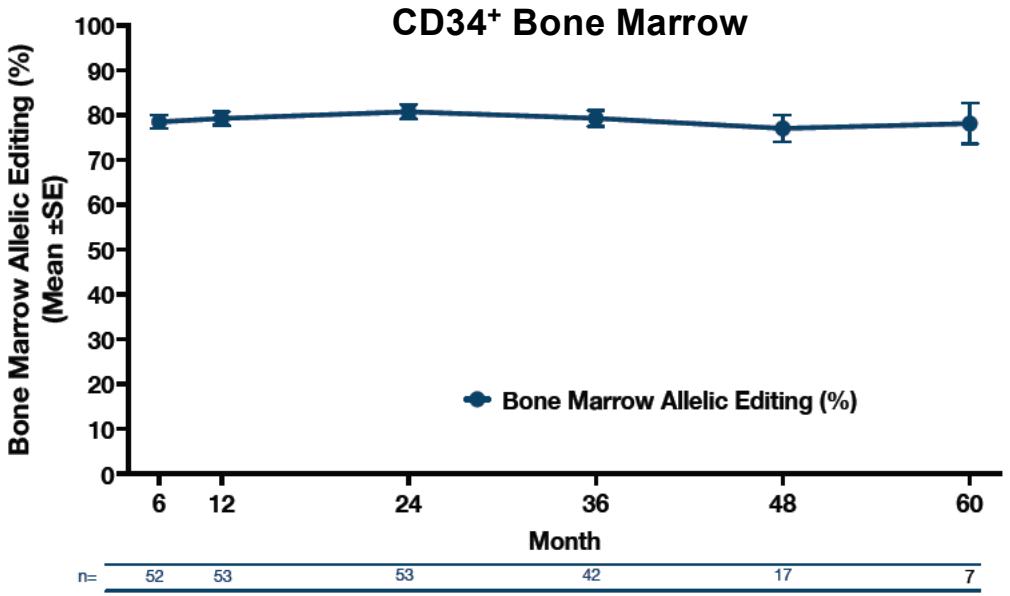
Durable Increases in Mean Total and Fetal Hemoglobin

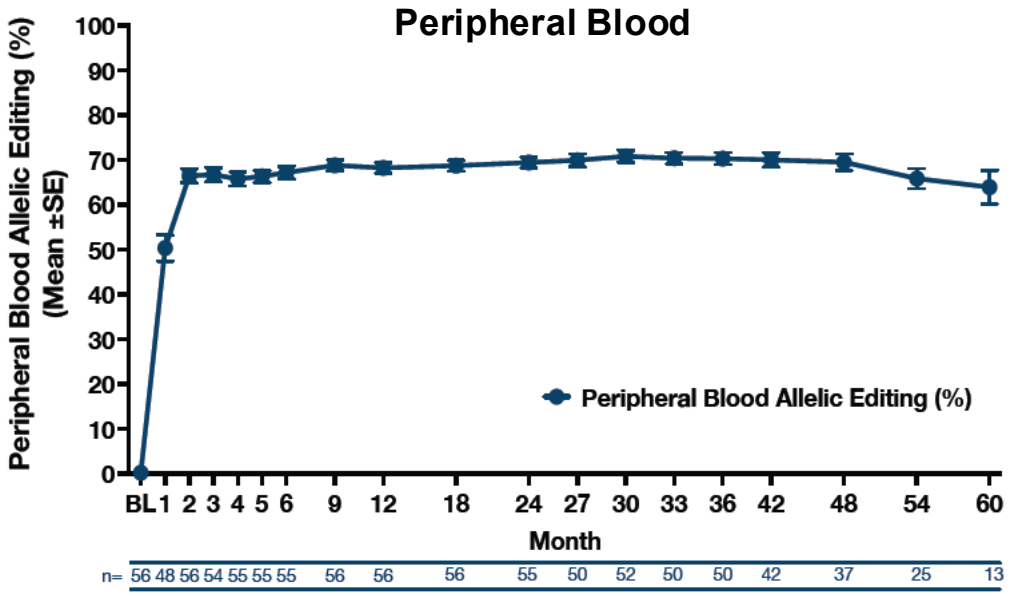


- Normal or near normal levels of total Hb
- Durable high (>95%) proportion of red blood cells containing HbF (F-cells) observed after exa-cel

Data shown as of Nov 2025
Figure depict data for all timepoints where ≥5 participants have completed the specified visit
BL: baseline; **Hb:** hemoglobin; **HbF:** fetal hemoglobin; **SE:** standard error

Durable Bone Marrow and Peripheral Blood Allelic Editing

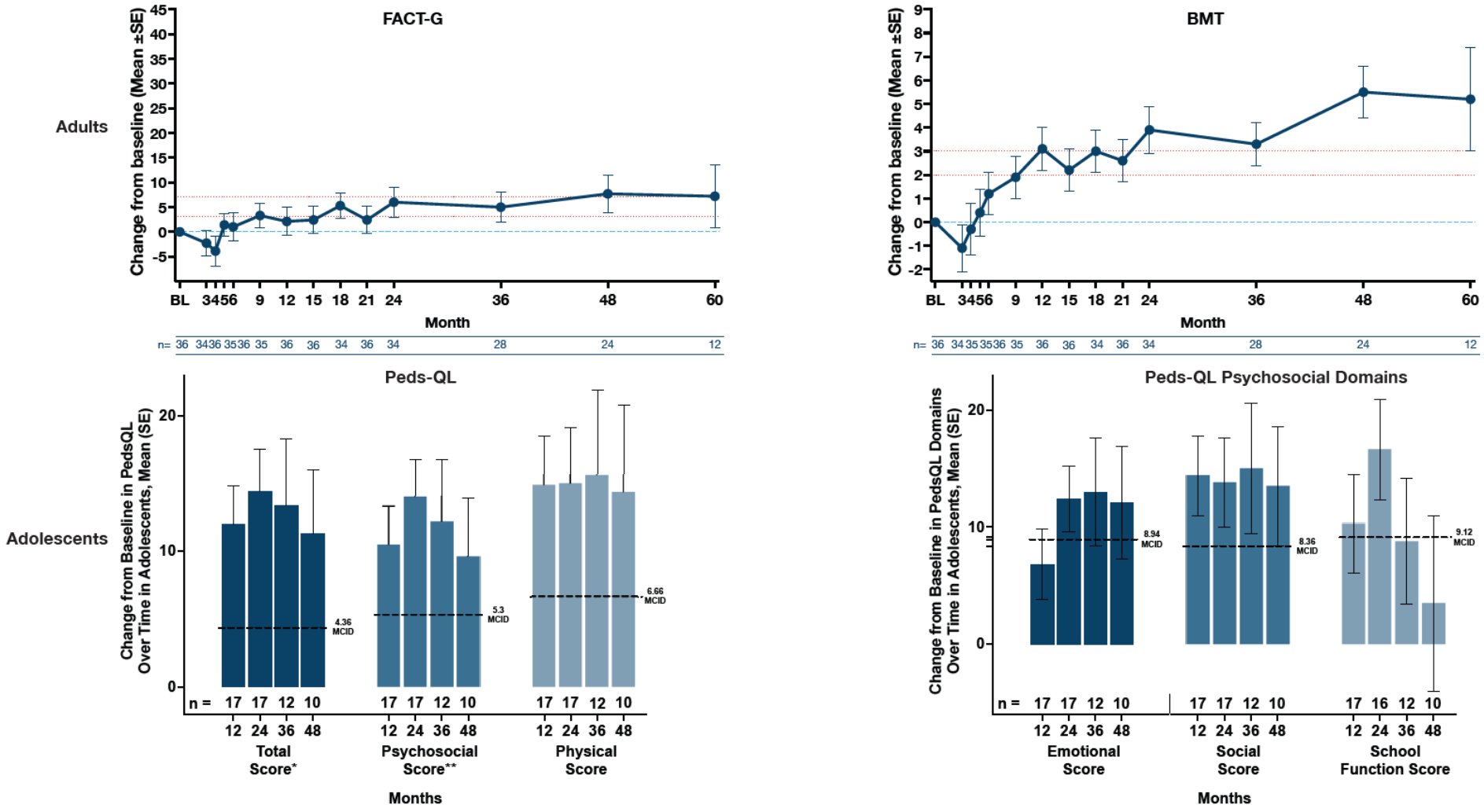




Data shown are as of Nov 2025
Figures depict data for all timepoints where ≥5 participants have completed the specified visit
BL: baseline; **HSCs:** hematopoietic stem cells; **SE:** standard error

- Successful editing of long-term HSCs consistent with durable clinical benefit
- Mean allelic editing of CD34+ cells in the bone marrow and peripheral blood was stable for up to 5 years of follow-up

Durable Improvements in Patient-Reported Outcomes



- Adults and adolescents had early and clinically meaningful improvements that were generally maintained across PRO tools and subscales

Data shown are as of Nov 2025

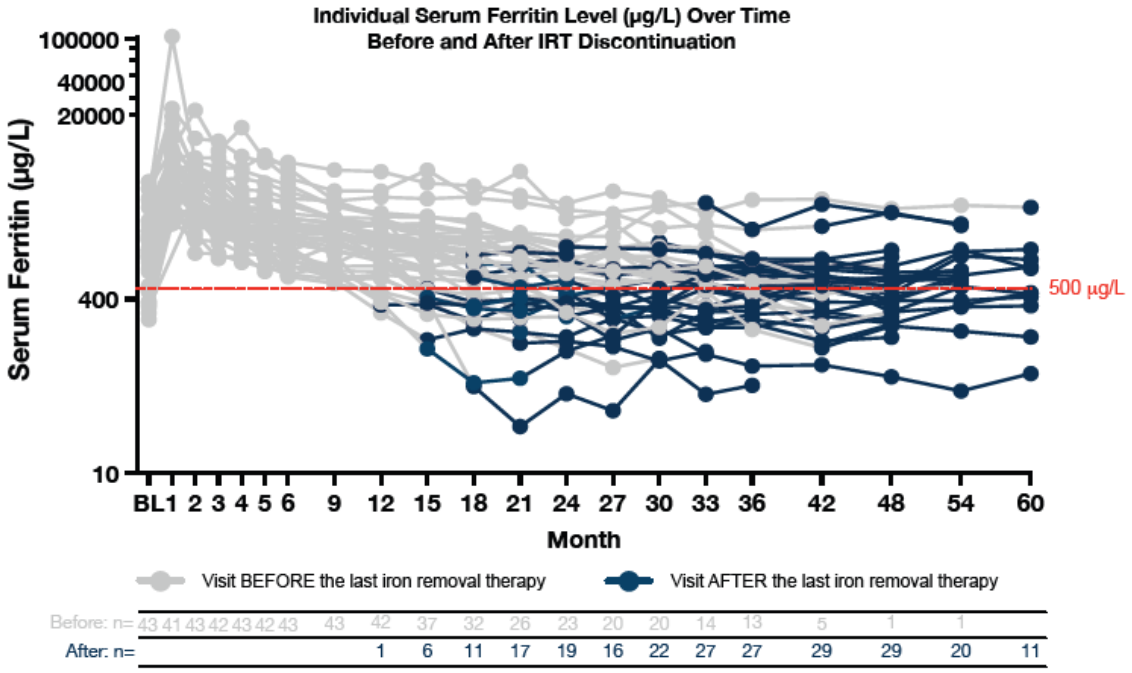
For FACT-G and BMT, red dashed lines depict established MCID range. For PedsQL and PedsQL Psychosocial domains, dashed lines indicated MCID for each measure.

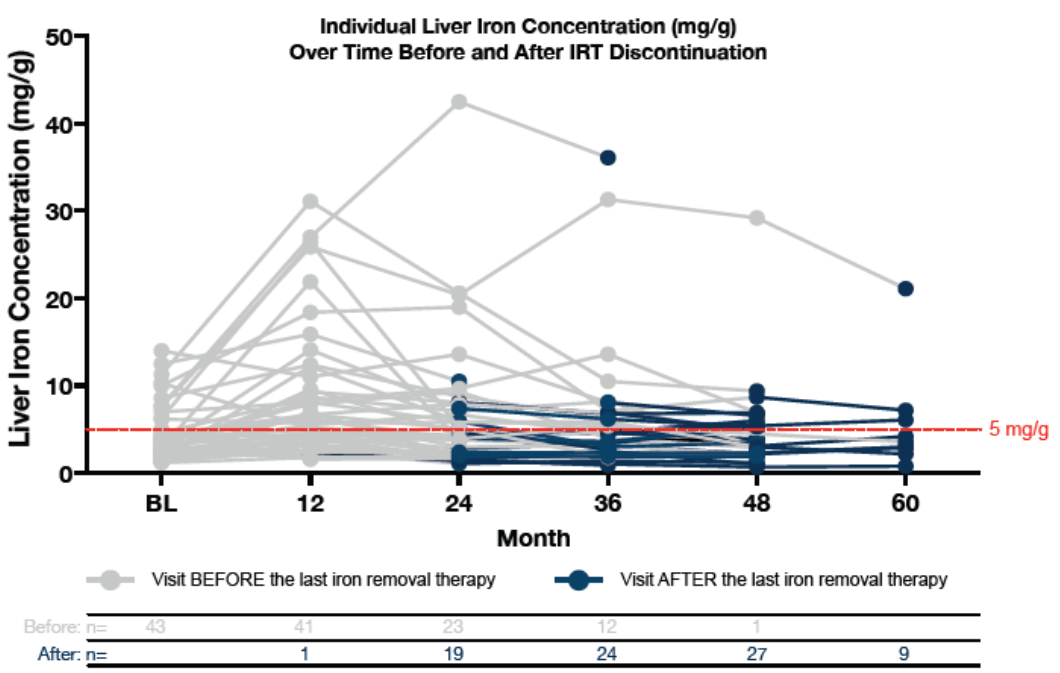
*Total score summarizes questions from the psychosocial and physical scores. **Psychosocial score summarizes questions from the emotional, social, and school function domains.

BL: baseline, **BMT**: bone marrow transplant, **FACT-G**: Functional Assessment of Cancer Therapy General, **MCID**: minimal clinically important difference, **PedsQL**: Pediatric Quality of Life Inventory, **PRO**: patient-reported outcome, **SE**: standard error

Durable Restoration of Iron Homeostasis: Serum Ferritin and Liver Iron Concentration Remain Stable After Discontinuation of Iron Removal Therapy

- As expected, all participants (56/56) resumed iron removal therapy (IRT) after exa-cel
- 77% (43/56) participants were able to stop IRT for ≥6 months at the time of this datacut
- Among the participants who discontinued IRT for ≥6 months:
  - Median time off of IRT was 25.2 months (range: 6.1 to 71.9)
  - No evidence of re-accumulation of tissue iron; liver iron concentration (LIC) remained stable after IRT discontinuation and no progressive increase in ferritin
  - Erythroferrone and hepcidin levels remained stable at levels consistent with normalized erythropoiesis





Data shown are as of Nov 2025.
Red dashed line indicates protocol recommended threshold for discontinuing IRT: serum ferritin = 500 µg/L; LIC = 5 mg/g.
BL: baseline, **exa-cel:** exagamglogene autotemcel, **IRT:** iron removal therapy

Exa-cel Safety Profile is Consistent with Busulfan Myeloablative Conditioning and Autologous HSCT in CLIMB THAL-111

Table 2. AE Overview in CLIMB THAL-111

Participants with	Exa-cel N = 56
Any AEs, n (%)	56 (100.0)
AEs related to exa-cel, n (%)[a]	16 (28.6)
AEs related to busulfan, n (%)[a]	55 (98.2)
AEs Grade 3/4, n (%)	50 (89.3)
SAEs, n (%)	19 (33.9)
SAEs related to exa-cel, n (%)[a]	2 (3.6)[b]
SAEs related to busulfan, n (%)[a]	9 (16.1)
AEs leading to death, n (%)	0
Any malignancies, n (%)	0

Data shown are as of Nov 2025.
All participants engrafted neutrophils and platelets. Data are presented from exa-cel infusion to Month 24.
[a] Includes related and possibly related AEs (or SAEs).
[b] Two participants had SAEs related to exa-cel (all resolved): 1 participant with hemophagocytic lymphohistiocytosis (HLH), headache, acute respiratory distress syndrome, and idiopathic pneumonia syndrome (latter also related to busulfan) all in the context of HLH; 1 participant with delayed engraftment and thrombocytopenia (both also related to busulfan).

AE: adverse event; **exa-cel:** exagamglogene autotemcel; **SAE:** serious adverse events

- The most common AEs occurring in ≥40% of participants from exa-cel infusion through Month 24 in CLIMB THAL-111 were febrile neutropenia, headache, stomatitis, anemia, nausea, thrombocytopenia, abdominal pain, vomiting, and mucosal inflammation.
- 7 (12.5%) participants had venoocclusive liver disease events
  - All events were related to busulfan conditioning (6 pts had q24 schedule)
  - All events resolved without any participant receiving ventilatory support or dialysis
- Majority of AEs occurred in the first 6 months after exa-cel infusion
- In CLIMB-131, of 55 participants enrolled, there were no participants with AEs related to exa-cel; 8 (14.5%) had SAEs (none related to exa-cel)
- There were no malignancies or deaths

CONCLUSIONS

- Exa-cel is the first and only approved CRISPR/Cas9 gene editing therapy[1]
- End of study results for CLIMB THAL-111 and follow-up in CLIMB-131 demonstrates that all participants achieved durable clinical benefit for up to 6.9 years of follow-up
  - 98% (55/56) achieving TI12 in CLIMB THAL-111 and CLIMB-131 combined, with a mean transfusion-free duration of 4.0 years
  - Durable increases in HbF resulting in total hemoglobin at normal or near normal levels
  - Stable allelic editing in bone marrow and peripheral blood demonstrating durable editing of long-term HSCs
- Exa-cel has the potential to prevent tissue iron accumulation via correction of underlying ineffective erythropoiesis
  - 77% of participants were able to discontinue iron removal therapy (IRT) for ≥6 months after exa-cel
  - No evidence of iron re-accumulation after IRT cessation with no observed progressive increases in LIC or ferritin for up to 6 years of available follow-up after IRT
- Safety profile is consistent with busulfan myeloablative conditioning and autologous transplant; no malignancies

Long term follow-up continues to demonstrate that exa-cel has the potential to provide a one-time functional cure to patients with TDT

1. Refer to regional label for specific indication

ACKNOWLEDGMENTS

Many thanks to trial participants & their families, as well as sites, investigators, nurses, and the entire exa-cel team

The authors acknowledge the site investigators

Mattia Algeri	IRCCS, Ospedale Pediatrico Bambino Gesù Rome
Maria Domenica Cappellini	University of Milan
Ben Carpenter	University College London Hospitals NHS Foundation Trust
Yogi Chopra	Hospital for Sick Children, Toronto
Selim Corbacioglu	Regensburg University Hospital
Josu de la Fuente	Imperial College Healthcare NHS Trust, St Mary's Hospital
Haydar Frangoul	Sarah Cannon Research Institute at The Children's Hospital at TriStar Centennial
Stephan A. Grupp	Children's Hospital of Philadelphia
Rupert Handgretinger	Children's University Hospital, Tubingen
Antonis Kattamis	National and Kapodistrian University of Athens
Melanie Kirby-Allen	Hospital for Sick Children, Toronto
Kevin H. M. Kuo	Toronto General Hospital, Toronto
Janet L. Kwiatkowski	Children's Hospital of Philadelphia
Peter Lang	Children's University Hospital, Tubingen
Amanda M. Li	BC Children's Hospital, University of British Columbia, Vancouver
Robert I. Liem	Ann and Robert Lurie Children's Hospital of Chicago
Franco Locatelli	IRCCS, Ospedale Pediatrico Bambino Gesù Rome, Catholic University of the Sacred Heart
Markus Mapara	Columbia University Medical Center
Roland Meisel	University Hospital Dusseldorf
Hayley Merkeley	The University of British Columbia/Adult Red Cell Disorder Program of British Columbia, Vancouver
Joachim Rupprecht	Children's University Hospital, Tubingen
Ami J. Shah	Stanford University
Sujit Sheth	Joan and Sanford I Weill Medical College of Cornell University
Sandeep Soni	Stanford University
Alexis Thompson	Ann and Robert Lurie Children's Hospital of Chicago
Donna Wall	Hospital for Sick Children, Toronto
John Wu	BC Children's Hospital, University of British Columbia, Vancouver

Medical writing and editorial coordination was provided by Linda Valsdottir, MS who is an employee of Vertex Pharmaceuticals Incorporated and holds stock and/or stock options at the company

Graphic support was provided by Patrick Coughlin who is an employee of Vertex Pharmaceuticals Incorporated and holds stock and/or stock options at the company

The **CLIMB THAL-111** trial was sponsored by Vertex Pharmaceuticals Incorporated and CRISPR Therapeutics